Table 1. Studies providing empirical evidence for the relationship between KE5 (Event 1500) and KE6 (Event 1501). +: Severity of Response. References available in main KER page.

Stressor (Reference)	**In vitro/in vivo/ex vivo**	**Species/Cell line**	**Exposure Conditions**	**KE5 (Event 1500) Increased, fibroblast proliferation, and myofibroblast differentiation**				**KE6 (Event 1501) Increased, extracellular matrix deposition**
Diphtheria toxin (Osterholzer et al., 2013)	In vivo	C57BL/6 mice WT Diphtheria toxin receptor (DTR) + mice $DTR^{+}/CCR2^{-/-}$ mice	10.0 μg/kg intraperitoneal injection once/day, 14 days. Evaluation: 7, 14, 21, days after onset of treatment.	Exudate macrophages (ExM) increased in DTR+ lungs	Accumulation of ExM and Ly-$6C^{high}$ monocytes in DTR+ lungs	Immunophenotype of ExM and $Ly6C^{high}$ monocytes in DTR+ mice		Lung collagen content in DTR+ mice
				Day 7: +++ Day 14: +++ Day 21: ++	Day 14: ++	Day 14: Expression mRNA or protein: Arginase, iNOS, IL-13 and TFG-β, CD45+, Col1+ and CCR4.		Day 21: increase hydroxyproline content
SiO_2 (Fang et al., 2018)	In vivo	Stock TEK-GFP 287 Sato/JNju (Tie2-GFP) mice	0.5 g/Kg intratracheal instillation. Evaluation: 28 days post exposure	Day 28: GFP localized with α-SMA/Acta2 in lung tissue				Day 28: Sirius red staining (marks collagen I and III) co-localized with GFP signal.
	In vitro	Mouse microvascular lung cells (MML1)	50 μg/cm^2 for 6, 12, 24, 48 h.	Increase protein expression of mesenchymal markers (Col1A1, Acta2)	Decrease protein expression of endothelial markers (Cdh5, PECAM1)	Increase cell proliferation and migration		
				6 h: 12 h: + 24 h: ++ 48 h: +++	6 h: 12 h: + 24 h: + 48 h: ++	6 h: 12 h: 24 h: + 48 h: ++		
	Human	Lung sections from patients	Patients with silicosis					Day 28: Decrease Tie2-GFP and HECTD1 expression
MWCNT (Dong et al., 2017)	In vivo	Male C57BL/6J WT mice B6.129S4-Timp1tm1Pds/J (Timp1 KO) mice	40 μg/mouse pharyngeal aspiration. Evaulation: 1, 3, 7, 14 days post exposure	Timp1 mRNA and protein levels increased in lung, BALF and serum	Increase FN1 protein expression in lungs	Increase FSP protein expression in lungs	Increase Ki67 and PCNA expression levels in lungs	Collagen deposition (Masson's trichrome)

				Day 1: +++ Day 3: +++ Day 7: ++ Day 14: +	Day 1: ++ Day 3: +++ Day 7: +++ Day 14: +	Day 1: + Day 3: +++ Day 7: +++ Day 14: ++	Day 1: + Day 3: ++ Day 7: +++ Day 14: ++	Day 1: + Day 3: ++ Day 7: +++ Day 14: ++
				Day 7: Increase in the levels of Hsp47, vimentin, α-SMA, PDGFR-β, CD63, integrin β1, p-Erk1/2, and genes involved in cell cycle regulation (WT and Timp1KO).				Day 7: Mice Timp1KO showed a significant reduction of fibrosis as compared to WT.
CeO_2 nanoparticles (Ma et al. 2017)	In vivo	Male Sprague-Dawley rats	0.15-7 mg/Kg intratracheal instillation Evaluation: 1 – 28 days post exposure	Increased soluble collagen in BALF			Increased α-SMA expression in lung tissue	Increases hydroxyproline content in lung tissue
				3.5 mg/Kg Day 3: + Day 28: +++			3.5mg/Kg Day 1: +++ Day 3: ++ Day 28:	Day 28 3.5 mg/Kg: + 7 mg/Kg: +
	Ex vivo	Alveolar Macrophages Fibroblasts ATII cells	Isolated from CeO2 exposed rats 1 - 28 days post-exposure	Increased TGF-β1 (Macrophages)	Decreased proliferation (Fibroblasts)	Increased α-SMA (Fibroblasts & ATII)		
				3.5mg/Kg CeO_2 Day 1: Day 3: ++ Day 10: ++ Day 28: +	Day 28 0.15mg/kg: + 1mg/kg: ++ 3.5mg/kg: +++ 7 mg/Kg: +++	Day 3 (ATII) 3.5mg/kg: +++ Day 28 (Fibroblasts) +++		
Bleomycin (Hu et al., 2015)	In vivo	Notch1 conditional knockout (CKO) and WT mice	2 U/kg endotracheal injection (WT & CKO mice) Evaluation: 7 – 28 days post exposure	Increased protein expression Jagged1 and Notch1 in WT mouse lungs	Increased expression mRNA α-SMA and Col1, Notch1 protein in isolated WT lung fibroblasts	Increased percentage of α-SMA+ cells in lungs		Increased hydroxyproline content in lung tissue

				Jagged1 Day 7: ++ Day 14: ++ Day 21: + Day 28: + Notch1 Day 7: ++ Day 14: + Day 21: - - - - Day 28: - - - -	Day 14 α-SMA (protein & mRNA): +++ Col1 (protein & mRNA): +++ Notch1(protein):	Day 14 WT mice: +++ CKO mice: +	Day 28 CKO mice showed a significant attenuation of collagen deposition as compared to WT.	
Bleomycin TGF-b (Blaauboer et al., 2014)	In vivo	Female C57BL/6 mice	30 μl (1.25 U/ml in PBS) Bleomycin intratracheal instillation. Evaluation: 1 – 5 weeks post exposure.	Increased α-SMA protein level on histological staining in lungs			New collagen formation and gene expression	Extracellular matrix proteins Increased protein level on histological staining in lungs
				Week 1: ++ Week 2: +++ Week 3: +			Gene expression of elastin, type V collagen and tenascin C highly correlated to new collagen formation	Elastin Week 1: + Week 2: ++ Week 3: +++ Type V collagen and tenascin C Week 1: +++ Week 2: ++ Week 4: ++
	In vitro	Primary normal human lung fibroblast (NHLF) Human fetal lung fibroblast (HFL-1)	1, 2, 4, 10 ng/mL TGF-β Evaluation: 24, 48 h	Increased mRNA expression 24 h	Increased ELN, COL5A1 mRNA expression 24 h	Increased mRNA expression 48 h, elastin coated surface		

									(10 ng/ml TGF-b)	
				ACTA 1: 2: + 5: ++ 10: +++	COL1A1 1: + 2: ++ 5: ++ 10: +++	ELN 1: + 2: ++ 5: +++ 10: ++++	COLSA1 1: 2: + 5: ++ 10: +++	TNC 1: 2: + 5: + 10: +++	+++ (ACTA2 COL1A1 ELN)	
Radiation (Judge et al., 2015)	Study population/ In vivo/In vitro	Lung biopsies from patients with thoracic radiation for cancer treatment C57BL/6 mice Primary human lung fibroblast	5 Gy total body plus 10 Gy thoracic radiation (mice). Evaluation: 12-26 weeks post exposure 3, 7 Gy (primary human lung fibroblasts) Evaluation: 5 days post exposure	Increased LDH expression		Increased extracellular acidification and lactate production (Fibroblasts)		Increased α-SMA protein expression, soluble collagen I, Col1A1, and Col3A1 mRNA levels (Fibroblasts)	TGF-β1 activation (Fibroblasts)	Increased collagen fibers deposition trichrome stain
				Lung biopsies: ++++ Mouse lung: Week 12: Week 16: + Week 18: + Week 26: +++ Fibroblasts: 3 Gy: 7 Gy: +++		Acidification 3 Gy:++ 7 Gy:+++ Lactate: 3 Gy: + 7 Gy: ++		Soluble Collagen 3 Gy: 7 Gy: +++ Col1A1 7 Gy: +++ Col3A1 7 Gy: +++	3 Gy: +++ 7 Gy: ++++	Lung biopsies: +++
Copper oxide nanoparticles (Lai et al. 2018)	In vivo	C57BL/6 mice	1, 2.5, 5, 10 mg/Kg intranasal instillation Evaluation: 7, 14, 28 days post exposure	Increased mRNA levels of CCL-2, CCL-3, IL-4, IL-10, IFN-α, TGF-β1 at day 14.		Cell apoptosis in lung tissue		Increased TGF-β1 content in BALF at day 14	Increased α-SMA at day 28	Increased collagen-I and hydroxyproline content at day 28

				5: +++	Day 14: 1: + 2.5: ++ 5: +++ 5mg/kg: Day 7: ++ Day 14: +++ Day 28: +++	2.5: +++ 5: ++++	2.5: ++ 5: ++++	2.5: ++ 5: +++
Cadmium chloride (Li et al., 2017)	In vivo	C57BL/6 vimentin knockout mice C57BL/6 WT mice	0.009, 0.018 mg/Kg intratracheal instillation (once / 2 days; 8 weeks) Evaluation: weeks 1, 2, 4, 8 of exposure.	Increased α-SMA in lung tissue (0.009 mg/Kg)				Increased (0.009 mg/Kg)
				Week 4: +++				Subepithelial thickness Week 4: ++ Airway resistance Week 4: ++ Collagen-I staining Week 4: +++ Picro-siruis red Week 4: +++ Collagen content (Sircol assay) Week 1: Week 2: ++ Week 4: ++ Week 8: +++
	In vitro	Primary human fibroblast	5, 10, 20 μM for 3 h. Allowed to recover for 3, 24, 48, 72 h.	Increased α-SMA				Increased
				10uM CdCl2 for 3 h followed by recovery 3 h: 24 h: 48 h: + 72 h: ++ 20uM CdCl2 for 3 h followed by recovery 3 h: + 24 h: + 48 h: ++				Soluble collagen (48 h recover) 5: 10: +++ 20: ++++ Soluble collagen (20uM CdCl2) 3 h: 24 h: ++++

				72 h: ++	48 h: ++++ 72 h: ++++ Fibronectin and Collagen I (10 & 20uM CdCl2) 3 h: + 24 h: ++ 48 h: +++ 72 h: +++